losporin derivatives, this effect is offset by the high serum levels achievable with therapeutic doses. There is evidence that some strains of *S. aureus* may develop resistance to the drug. There is not yet sufficient data to assess the extent or importance of this phenomenon.

Dosage and Administration—Tentative adult dosage is 250 to 500 mg three to four times daily. Food in the stomach interferes with absorption. A single 500 mg dose taken in the fasting state produced an average peak serum level of 18 mcg/ml in 12 adults. Approximately 70-80% of the drug is excreted unchanged into the urine within four hours of oral administration on an empty stomach.

Toxicity and Side Effects—There is little data on toxicity, but it appears that increased frequency of bowel movements or diarrhea may occur. There is no information concerning possible nephrotoxicity in clinical usage. Allergy to other cephalosporin derivatives, and perhaps to penicillin as well, may make allergic response to cephalexin likely.

Rifampicin (Rifampin)

Rifampicin (rifampin) is the amino methyl piperazine derivative of rifamycin S.V. The naturally occurring rifamycins from which this drug is derived were first isolated from cultures of *Streptomyces mediterranei* in 1959. It is unrelated chemically to other commonly available antibiotics. The mechanism of action is not fully understood but there is no evidence that it interferes with the synthesis of either cell wall, protein or nucleic acid. Unlike the parent rifamycin S.V., rifampicin is effective orally.

Antimicrobial Activity—The minimum inhibitory concentrations (MIC) for most strains of *Staphylococcus aureus, Streptococcus pyogenes,* and *Diplococcus pneumoniae* are very low (<0.5 mcg/ml). The MIC for Gram-negative pathogens and for enterococcus is higher but many strains are inhibited by 10 mcg/ml or less. The manufacturer is presently restricting investigational use to therapy of mycobacterial and gonococcal infections. All strains of *M. tuberculosis var. hominis* examined were inhibited by levels of 1 mcg/ml or less. Atypical mycobacteria are also often susceptible.

The significance of a potential problem of early development of resistance on the part of some microorganisms remains to be determined.

Dosage and Administration — Rifampicin is available for oral use only. The usual adult dose is 300 mg tid, preferably on an empty stomach. A peak level of 3 to 5 mcg/ml is reached two to three hours after a single 300 mg dose and the level at 12 hours is not measurable. The drug is excreted primarily into the bile, but ten percent to 15 percent is recovered in the urine.

Toxicity and Side Effects — Granulocytopenia (apparently reversible) has been reported. Rarely, mild headache and gastrointestinal complaints have been observed.

Saramycetin

Saramycetin is an anti-fungal drug which has been known previously by the code designations RO 2-7758 and X-5079C. It is a polypeptide produced by a species of *Streptomyces.* Technical difficulties have limited the availability of this drug markedly despite the length of time it has been known.

Antimicrobial Activity—This drug appears to have a clinically useful level of activity for the treatment of infections caused by *Blastomyces dermatitidis* and *Histoplasma capsulatum,* and to a lesser extent *Sporotrichum schenkii.* Activity against *Coccidioides immitis* is of questionable usefulness, and it is ineffective in *Cryptococcus neoformans* infections.

Dosage and Administration—Usual dose reported is 3 to 5 mg/kg/day subcutaneously for periods of four to six weeks.

Toxicity and Side Effects—Alteration in liver function tests was almost universal in patients treated. Results of liver function tests usually returned to normal in patients without pre-treatment abnormalities of liver function. Pre- and post-treatment liver biopsies have shown variable tissue changes. Other side effects of treatment that have been observed are eosinophilia, local pain and inflammation at injection site, febrile reactions and urticarial reactions.

ANTIBACTERIAL AGENTS IN RENAL INSUFFICIENCY

IRWIN ZIMENT, M.B., M.R.C.P.

1. Excretion of Antibacterial Agents:

Most antibiotics and chemotherapeutic agents, and their degradation products, are excreted mainly by the kidneys, thus necessitating reduc-

TABLE 1.—*Dosage Modifications Required in Renal Insufficiency.*
(Tabulation of the antibacterial agents on the basis of renal and extra-renal toxicity as determinants for dosage modification in renal insufficiency.)

MAJOR MODIFICATION			MINOR MODIFICATION	NO MODIFICATION	CONTRA-INDICATED
Major Renal Toxicity		*? Renal Toxicity*	*No Renal Toxicity*	*(Avoid High Dosage)*	
Major Extra-Renal Toxicity	*Minor or No Extra-Renal Toxicity*	*Major Extra-Renal Toxicity*	*Some Extra-Renal Toxicity*		
Kanamycin	Polymyxin	Streptomycin	Chloramphenicol	Penicillin‡	Nitrofurantoin
Gentamicin	Colistin	Tetracycline*	Lincomycin**	Ampicillin	Nalidixic acid
Neomycin†	Bacitracin†	Oxytetracycline*	Cephalothin**	Methicillin***	Methenamine
Vancomycin	Cephaloridine†	Chlortetracycline*	INH	Other penicillins	Long-acting sulfonamides
Amphotericin			PAS†	Erythromycin	
(? Short-acting sulfonamides)			Cycloserine (? Ethambutol)	Novobiocin	Long-acting tetracyclines

*Intravenous tetracycline causes higher peak blood levels and such therapy is more hazardous than oral dosage. Particular caution should be observed in pregnant women. Out-dated tetracycline products should never be used, since rare cases of the Fanconi syndrome have resulted; this occurred particularly under moist storage circumstances in products containing citric acid in the formulation. Chlortetracycline is rarely used now.

**Cephalothin and lincomycin do not appear to be toxic in renal failure, but lower dosage is recommended since retention of the drugs occurs, making usual dosage regimens excessive.

***Methicillin has caused hypersensitivity nephrotoxic reactions. Large dose therapy can introduce an appreciable sodium load, which could be dangerous in renal failure.

†These agents should be avoided in uremic patients.

‡Large dose penicillin therapy in renal failure can introduce a dangerous electrolyte load, and also carries a marked risk of neurotoxicity.

tion of dosage in patients with renal insufficiency. This is important not only in the case of nephrotoxic drugs, but also for those drugs which have major extrarenal toxicity. Reduced dosage is also desirable for most non-toxic antibacterial agents which are cleared by the kidney, since normal dosage would produce accumulation in the body, whereas lower dosage regimens offer advantages in economy and ease of administration with less risk of superinfection.

The appropriate dosage to administer is based upon whether or not the drug is excreted by the kidney:

(1) *Cleared mainly by the kidney:*

(a) *Major nephrotoxic agents:* kanamycin, neomycin, gentamicin, polymyxin, colistimethate, vancomycin, cephaloridine, sulfonamides, amphotericin, bacitracin

(b) *Possibly nephrotoxic agents:* tetracycline, streptomycin

(c) *Non-nephrotoxic agents* (in usual dosage):

(i) No extra-renal toxicity: penicillin, methicillin, ampicillin, oxacillin, cloxacillin, dicloxacillin, nafcillin, cephalothin, lincomycin

(ii) Some extra-renal toxicity: INH, PAS

(2) *Not cleared by kidney* (in unchanged form):

(a) *Potentially toxic:* chlortetracycline, chloramphenicol

(b) *Non-toxic:* erythromycin, novobiocin

For dosage modifications see Tables 1 and 2.

2. Antibacterial Agents Contraindicated in Renal Failure:

a. *The antituberculosis drugs* — Pyrazinamide, ethionamide, cycloserine, viomycin and ethambutol are best avoided in patients with marked renal impairment. Only viomycin is nephrotoxic, but the others all have marked extrarenal toxicity. No dosage schedule for use of these second-line drugs in renal failure can be recommended as safe since information in this area is inadequate; only INH, streptomycin, PAS, and possibly ethambutol and cycloserine should be used. INH appears to be very safe in azotemia unless the patient is malnourished or alcoholic; in such cases reduced INH dosage with pyridoxine supplements is advisable. Many uremic patients have difficulty tolerating PAS, and unless its use is considered to be essential, it should be avoided in severe renal insufficiency. Streptomycin should be used with appropriate dosage reduction in uremia; elderly patients are particularly liable to suffer toxic effects, and should be carefully monitored.

b. *Agents used for urinary tract infections*—

(1) *Sulfonamides* should not be used in patients who cannot maintain adequate fluid intake or when renal insufficiency is present. The dangers of crystalluria and extra-renal toxicity make these drugs unsuitable, unless therapy can be carefully controlled.

(2) *Nitrofurantoin* and *nalidixic acid* are

TABLE 2.—*Antibiotic Dosage in Renal Failure*

Antibiotic	*Normal-36% Normal Renal Function (Normal Creatinine)*	*35%-10% Normal Renal Function (Creatinine 1.5-5.0)*	*9%-0% (Anuria) of Renal Function (Creatinine>5.0)*
Aq. Penicillin G	Normal dose depending on infection	Normal dose, but high dosage therapy contraindicated	
Ampicillin	Normal dose depending on infection	Normal dose	Normal dose
Oxacillin (IM or IV)	Normal dose depending on infection	Normal dose	0.25-1.0 Gm q 6 h
Cloxacillin (oral)	Normal dose depending on infection	Normal dose	0.25-0.5 Gm q 6 h
Dicloxacillin	Normal dose depending on infection	Normal dose	0.25-0.5 Gm q 6 h
Methicillin	1.0-3.0 Gm q 3-6 h	1.0-2.0 Gm q 3-6 h	1.0-2.0 Gm q 4-8 h
Nafcillin	0.25-3.0 Gm q 3-6 h	0.25-1.0 Gm q 3-6 h	0.25-1.0 Gm q 3-6 h
Cephalothin	1.0-3.0 Gm q 3-6 h	1.0-2.0 Gm q 6-8 h	1.0 Gm q 6-24 h
Cephaloridine	0.25-1.0 Gm q 6 h	Do not use	Do not use
Lincomycin (oral)	0.5 Gm q 6-8 h	0.25 Gm q 6-8 h	0.25 Gm q 8-12 h
Lincomycin (IM, IV)	0.6 Gm q 8-12 h	0.3 Gm q 8-12 h	0.2 Gm q 8-12 h
Erythromycin	0.25-0.5 Gm q 6 h	0.25-0.5 Gm q 6 h	0.25-0.5 Gm q 6 h
Novobiocin	0.25-0.5 Gm q 6 h	0.25-0.5 Gm q 6 h	0.25-0.5 Gm q 6 h
Tetracycline and Oxytetracycline (oral)	0.25-0.5 Gm q 6 h	1st day: 0.25 Gm q 6 h Then: 0.5 Gm q 1-2 days (do not give intravenously)	1st day: 0.25 Gm q 6 h Then: 0.5 Gm q 3-4 days
Chlortetracycline (oral)	0.25-0.5 Gm q 6 h	0.25-0.5 Gm q 6 h	Use not advised
Chloramphenicol	0.25-1.0 Gm q 6 h	0.25-1.0 Gm q 6 h	(?) Normal dose
INH	300 mg q.d. (in 1 dose)	100 mg q 8 h + pyridoxine	(?) 100 mg qd + pyridoxine
PAS	4 Gm t.i.d.	2 Gm t.i.d.	Do not use
Neomycin (oral)	1.5 Gm q 4-6 h	Do not use	Do not use
Kanamycin (oral)	1.5 Gm q 4-6 h	1.0 Gm q8-12h	Do not use
Kanamycin (I.M.)	7.5 mg/kg/day q12h	1st day: 7.5 mg/kg q12h (x2) Then 7.5 mg/kg q1-2 days	1st day: 7.5 mg/kg (1 dose only) Then: 7.5 mg/kg q3-6 days
Streptomycin	0.5-1.0 Gm q12h	1st day: 0.5 Gm q12h (x2) Then 0.5 Gm q1-2 days	1st day: 0.5 Gm q12h (x2) Then: 0.5 Gm q3-4 days
Vancomycin	1 Gm q12h	0.5 Gm q2-3 days	1.0 Gm q10 days
Polymyxin (I.M., I.V.)	0.8 mg/kg q8h	1st day: normal dosage Then: 0.8 mg/kg q48h	1st day: normal dosage Then: 0.8 mg/kg q3d
Colistimethrate (I.M.)	1.6 mg/kg q8h	1st day: normal dosage Then: 1.6 mg/kg q36-38h	1st day: normal dosage Then: 1.6 mg/kg q3d
Gentamicin (I.M.)	0.3-1.5 mg/kg q8h-q12h	1st day: normal dosage Then: 0.3-1.0 mg/kg q12-24h	1st day: normal dosage Then: 0.3-1.0 mg/kg q3-4 days
Nitrofurantoin (oral)	100 mg q6h	Do not use	Do not use
Nitrofurantoin (I.V.)	180 mg q12h	Do not use	Do not use
Nalidixic acid	0.5-1.0 Gm q6h	Do not use	Do not use
Sulfonamides	Normal dose	Do not use	Do not use
Methenamine	1.0 Gm q6h (+ urine acidification to pH 5.0-5.5)	Do not use	Do not use
Amphotericin	1.0 mg/kg 3 x/week (Dosage depends on effect on creatinine clearance)	1.0 mg/kg 2 x/week	Unknown

specifically indicated for the treatment of urinary tract infections, but are only effective when renal function is normal, and should not be used otherwise since extra-renal toxicity may result.

(3) *Methenamine* is only effective in the treatment of urinary tract infections when the urine pH is reduced to 5-5.5 (e.g. by giving methionine). Acidification of the urine in renal failure may prove impossible, and systemic acidosis can result from giving acidifying drugs. Therefore, methenamine, although relatively non-toxic, is unsuitable for patients with renal insufficiency.

3. Principle in the Treatment of Infections in the Presence of Renal Insufficiency:

(1) The least nephrotoxic agent should always be selected, (preferably on the basis of bacteriologic susceptibility studies).

(2) A relatively non-toxic (all types of toxicity

considered) antibiotic should be given if suitable; e.g., penicillin G, ampicillin, penicillinase-resistant penicillins, erythromycin, cephalothin.

(3) A toxic agent should be given for as short a period as is consistent with effective eradication of the infection.

(4) Frequent serum creatinine levels and creatinine clearance, if possible, should be obtained to guide changes in drug dosage. Urine output should be watched.

(5) The patient's clinical response is as important a guide to dosage as are the recommendations in Table 2.

(6) Avoid long-acting preparations of penicillins, tetracyclines, sulfonamides or other drugs.

(7) *Chlortetracycline* is more readily inactivated than other tetracyclines. However, it may have a catabolic effect and therefore its use in the presence of azotemia is no longer advised.

(8) *Chloramphenicol* degradation products could accumulate in patients with renal insufficiency; it is still not clear whether or not these metabolites are toxic.

(9) *Sulfonamides* may present an added risk to the patient with renal insufficiency, although one study suggests that sulfadimidine is not retained and is effective therapy for urinary infections in the presence of azotemia.

(10) *Amphotericin* therapy induces renal defects in most recipients; while these are initially reversible, long-term intravenous administration often causes permanent damage, and a loss in renal function may have to be accepted if the fungal infection is to be effectively treated. The modification of dosage which may be necessary in patients with renal insufficiency is unknown.

4. Nephrotoxic Antibiotics in Renal Failure:

Severe infections in patients with renal failure may necessitate therapy with nephrotoxic agents, and the risk of further deterioration in renal function must be balanced against the dangers of the infection. Renal function may actually be improved if the infection is in the kidneys or if there is prerenal failure associated with systemic infection.

If the patient has end-stage renal disease, the further damage that may occur while using a nephrotoxic agent is relatively unimportant if the patient can subsequently be admitted to a chronic dialysis program. This applies in particular to the use of polymyxin or colistimethate whose extrarenal toxicity is not a major problem; however, high blood levels of these drugs may produce apnea (the other neurotoxic effects of the polymyxins are always reversible). Cephaloridine and bacitracin (which is rarely used) are likewise nephrotoxic, but differ from the polymyxins in having no extra-renal toxicity, and theoretically may be safely used in irreversible renal failure, whereas they should not be used if there is hope of renal improvement.

5. Treatment of Urinary Tract Infections:

This usually proves to be unsatisfactory in patients with chronic renal failure since the concentration of antibiotics in the urine, and possibly in the renal parenchyma, is generally inadequate. Treatment with the largest recommended dosage of the less toxic antibiotics should be tried, with repeated urine culture as a guide to the success of therapy.

It is of interest that the combination of penicillin or ampicillin with a penicillinase-resistant penicillin may occasionally give a synergistic bactericidal effect against a wide spectrum of bacteria including *Pseudomonas*. A return of infection is usual after antibacterial therapy is terminated, however.

It is important to remember that the effectiveness of many antibacterial agents may be very dependent upon the pH of the medium:

(1) *More effective in alkaline urine:* erythromycin, streptomycin, kanamycin, gentamicin, sulfonamides.

(2) *More effective in acid urine:* tetracyclines, novobiocin, cycloserine, nitrofurantoin, methenamine compounds.

(3) *Relatively independent of pH:* chloramphenicol, ampicillin, (?) polymyxins.

In the presence of renal insufficiency, attempts to alter the urinary pH may not be possible without serious changes in acid-base balance.

6. Evaluation of Renal Function:

The serum creatinine provides a good guide to renal status, and serial endogenous creatinine clearances provide the best guide to changes in renal function when using a nephrotoxic antibiotic. Even a barely elevated serum creatinine is consistent with a 75 percent loss of renal function. Restriction in dosage of drugs cleared by the kidney is required only when renal function is less than 35 percent normal. An initial creatinine determination should always be obtained prior to starting therapy with a nephrotoxic antibiotic and frequent creatinine determinations should be obtained during therapy, even in patients with no

known renal disease. Urine examination is not so helpful, since an abnormal sediment may appear during therapy without any significant damage to the kidney having occurred.

7. Extra-renal Toxicity of Antibacterial Agents:

The non-renal toxic effects of kanamycin, vancomycin, streptomycin, tetracyclines (especially intravenous), and possibly chloramphenicol and INH are an increased hazard when renal function is borderline. Monitoring of serum creatinine safeguards against inadvertent accumulation of these drugs when renal function is suspect. Kanamycin is a particular danger since rapid onset of hearing loss has followed in some patients with over-dosage; single dose therapy with this drug should not exceed 7.5 mg/kg since deafness has been recorded after a single dose of 1 Gm in a patient with renal impairment.

8. Antibiotic Serum Assays:

These are rarely performed by routine hospital laboratories, but should be helpful in patients with renal failure who are receiving potentially toxic agents. This applies both to nephrotoxic agents and to those with major toxicity in other areas.

It is unfortunate that such exact guidance can rarely be employed, since reliable and meaningful results can only be obtained from laboratories which do assays regularly. Further, assays take time, and the delayed results may not help in a critical case.

The therapeutic range for an antibiotic depends upon the particular infection and the toxic level is not always known. The following levels should prove therapeutically adequate, and should not be exceeded if toxic effects are to be avoided. (Blood samples should be taken about two hours after administering the drug):

Streptomycin 20-40 mcg/ml
Chloramphenicol 15-30 mcg/ml
Kanamycin 10-20 mcg/ml
Vancomycin 10-20 mcg/ml
Colistin 10-20 mcg/ml
Gentamicin 7-10 mcg/ml
Polymyxin 5-10 mcg/ml
Tetracycline 3-10 mcg/ml
INH 1-3 mcg/ml

It may also be useful to check the levels at periods of 24 hours after drug doses for a guide to possible adjustment in frequency of administration. When treating a urinary tract infection in renal insufficiency it may be useful to assay the urine to ensure that adequate amounts of the agent do get excreted. If insufficient amounts are excreted, then administering the agent may prove futile and introduces an unnecessary hazard. Assays of antibiotics in urine are simpler to perform than are serum assays.

9. Recovery Phase Following Acute Renal Failure:

The diuretic phase following acute renal shutdown is associated with persistence of the impairment of excretory function. Normal dosage of those antibiotics excreted principally by the kidney remains hazardous until the creatinine clearance has returned to normal. For practical purposes a creatinine clearance of less than 10 ml/min implies anuria.

10. Hepatorenal Failure:

The association of hepatic failure with renal insufficiency necessitates further reduction in dosage of certain of those antibiotics excreted or inactivated by the liver, i.e. ampicillin, tetracycline group, chloramphenicol, erythromycin (estolate), novobiocin, lincomycin and possibly cephalothin. In managing hepatorenal failure oral kanamycin is safer than neomycin, but either may accumulate to reach toxic levels in the blood. For further details see section on Antibiotics and Liver Disease.

11. Use of Antibacterial Agents in Patients on Dialysis:

Adjustments in antibiotic dosage may be required for anuric patients sustained on peritoneal dialysis or hemodialysis. Information is incomplete for many antibiotics, and *the following schedule is only an approximate guide.* Drugs not mentioned below should not be used since information on them is not available, and safer antibiotics can be used.

a. *Dosage as in anuria* (see Table 2):

(1) *Excreted or inactivated by non-renal mechanisms:*

erythromycin
chloramphenicol
(?ampicillin*)

(2) *Not removed by dialysis:*

polymyxin
colistin
vancomycin
lincomycin
oxacillin
cloxacillin
methicillin

*Information inadequate.

(?penicillin*)
(?dicloxacillin*)

b. *Minor dosage adjustment required* — for drugs which are partially removed by dialysis:

(1) *Hemodialysis*—dosage schedules are relatively well established for patients on chronic twice-weekly dialysis:

tetracycline (oral)	— 0.5 Gm post-dialysis
streptomycin	— 0.5 Gm post-dialysis
gentamicin	— 1 mg/kg post-dialysis
kanamycin	— 7.5 mg/kg post-dialysis
INH	— 300 mg post-dialysis, then 100 mg + pyridoxine q 24 h

(2) *Peritoneal dialysis* — Since long-term regular peritoneal dialysis is rarely used, guidelines for antibiotic dosage are less clearly established. Insufficient amounts of tetracycline are removed to be of significance, and the dosage recommended for the anuric patient should be used. More substantial amounts of kanamycin and streptomycin (and possibly gentamicin) are removed; the dosage suggested for patients on hemodialysis could be used, but the appropriateness of this is uncertain.

c. *Dosage adjustment probably required*—information not adequate:

amphotericin
cephalothin
cephaloridine

It should also be noted that dialysis (peritoneal or hemodialysis) should be used in the management of overdosage with kanamycin and possibly streptomycin and gentamicin, but is unlikely to be of value with other nephrotoxic antibiotic intoxications.

Antibiotics should not be added to the dialysing fluid used in peritoneal dialysis, since they are of no value as prophylaxis against infection and may get absorbed and accumulate in the body.

Table 2 provides an approximate guide to dosage for antibacterial agents in patients with renal insufficiency. Much of the information currently available is inadequate, and *this guide cannot be regarded as definitive.* It should be appreciated that in any individual patient such a dosage guide could result in inadequate or hazardous drug levels unless clinical and laboratory guides are obtained concurrently and appropriate dosage adjustments made as necessary.

*Information inadequate.

ANTIBIOTICS AND LIVER DISEASE

IRVIN JACOBS, M.D.

The following outline is an attempted compilation of known information to serve as a guide in using antibiotic therapy in patients with (a) underlying liver disease and (b) acute liver and gallbladder infections. Unfortunately, precise information is inadequate for many of the drugs. For some drugs very little human data is available for liver tissue antibiotic concentrations, liver histology during treatment, bile levels, and precise metabolic processes in the liver. Indeed, for many older drugs and drugs that are little used, even animal data is scanty.

It is emphasized that often animal data is not applicable to man. A good example is isoniazid, which given long term to dogs produces fatty changes and jaundice; this development is rare in man.

For the most part in treating patients with preexisting liver disease who develop infections outside the liver, one should use caution in prescribing drugs known to be dependent on liver for inactivation or excretion. Usually a safer substitute drug can be found. If a potentially toxic drug must be used, blood levels can be useful in monitoring the dose to within safe limits. One should also take care to avoid use of hepatotoxic non-antibiotic drugs concomitantly.

On the other hand, drugs metabolized and/or excreted by the liver are theoretically ideal for treatment of acute infections of liver and biliary tract.

I. Penicillin G

1. Metabolism by liver: Only minor fraction is ordinarily handled by liver, but in impaired renal function the liver may be a major excretion route via bile.

2. Liver tissue levels: Significant

3. Bile levels: Significant concentration

4. Liver toxicity: Rarely, as part of a generalized hypersensitivity reaction

5. Dose in liver disease:

(a) No change if renal function is good

(b) Reduce dose in circumstance of combined kidney and liver disease.

6. Comment: All penicillins are concentrated in bile even if absolute amount of hepatic excretion is small.